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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,686	08/03/2006	J. Christopher Anderson	54-000330US	8860

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EXAMINER	
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ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,686	ANDERSON ET AL.	
	Examiner	Art Unit	
	KAGNEW H. GEBREYESUS	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-13,15-19,21,22,36-40,42-50,52-55 and 59-64* is/are pending in the application.

4a) Of the above claim(s) *36-40,42-50,52-55 and 59-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-13,15-19,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/27/07, 6/21/07 and 9/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I: Claims 1-3, 6-13, 15-19, 21 and 22 are drawn to a translation system, or a cell that comprising an orthogonal lysyl tRNA (lysyl O-tRNA) or a modified variant thereof, an orthogonal aminoacyl tRNA synthetase (O-RS) or a modified variant that preferentially charges an orthogonal lysyl tRNA with one or more amino acid or with an unnatural amino acid, such as a homoglutamine.

Group II: Claims 36 are drawn to a composition comprising an ORS of PhΔAD or an ORS of I41 and/or S268 mutant of PhΔAD and variants thereof.

Group III. Claims 37 are drawn to a composition comprising polynucleotides encoding an ORS of PhΔAD and variants thereof or an I41 and/or S268 mutant of PhΔAD and variants thereof.

Group IV. Claim 38 is drawn to nucleic acids of SEQ ID O: 26 or a conservative variant thereof.

Group V. Claim 39, 40, 42-50, 53-55 is drawn to a composition comprising comprising an orthogonal aminoacyl tRNA synthetase (O-RS) that preferentially charges an orthogonal lysyl tRNA with a homoglutamine, with an efficiency of at least 50% that of an ORS corresponding to an I41 and/or S268 mutant of PhΔAD in aminoacylating an OtRNA corresponding to SEQ ID NO: 26.

Group VI. Claims 59-63 are drawn to a method of selecting an active ORS that loads a homoglutamine on an orthogonal tRNA, the ORS and a protein produced with the method wherein the ORS comprises, PhΔAD, an I41 and/or S268 mutant of PhΔAD, or a conservative variant thereof

Group VII. Claim 64 is drawn to a method of producing a protein in a cell with a homoglutamine at a specified position.
If applicants elect the invention of Groups I or Group V, they must also elect one species from the group:

(i) a translation system or a composition that incorporates at least one unnatural amino acid or;

(ii) a translation system or a composition that incorporates at least two unnatural amino acid into a protein.

The technical feature linking the inventions of group I-VI is a translation system comprising an orthogonal RS that preferentially aminoacylates an OtRNA with an unnatural amino acid. However this technical feature is not a special technical feature because a translation system comprising an ORS that preferentially aminoacylates an OtRNA with an unnatural amino acid was known in the art. Schultz et al (WO2002085923-A2) teach an in vivo translation system comprising an ORS that preferentially aminoacylates an OtRNA with an unnatural amino acid wherein said ORS/OtRNA were identified using a screening method. Thus the technical feature first claimed linking the the inventions of group I-VI is not a special technical feature as defined by PCT Rule 13.1.

During a telephone conversation conducted with Attorney Jonathan Quine, on April 14, 2008, an election of Group I comprising claims 1-3, 6-19, 21 and 22 was made with traverse. Furthermore Applicants elected species (i) a translation system or a composition that incorporates at least one unnatural amino acid into a protein.

Priority

Acknowledgment is made to this application which is a 371 of PCT/US04/022187 filed on July, 7, 2004 which claims benefit of 60/485,451, filed July 7, 2003 and further claims benefit of US provisional applications 60/528,815, filed on December 10, 2003 and 60/537,149 filed January 15, 2004.

Information Disclosure Statement

The information disclosure statement filed on June 21, 2007, February 27, 2007 and September 18, 2006 for which a copy of the patent publication has been submitted in this application has been considered as shown by the Examiners signature.

Oath/Declaration

The oath or declaration submitted on August 03, 2006 has been reviewed and is in compliance with 37 CFR 1.56.

Specification

The specification is objected to for an unclear incorporation by reference. In paragraphs [0184] and [0199] reference to a related case by attorney docket number is unclear. The Examiner suggests use of either the Patent Application Publication number of the other application (preferable) or the application number for clarity.

Group I comprising claims 1-3, 6-13, 15-19, 21 and 22 and species (i) a translation system or a composition that incorporates at least one unnatural amino acid into a protein is present for examination. Claims 36-40, 42-50, 52-55, 59-64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected groups, there being no allowable or linking claims.

Objection -Specification

Compliance with Sequence Rules

This application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below. In particular, 37 CFR 1.821 (d) states: "Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application".

In the instant case, the requirements are not met because, on page 69, primers CA510, CA511, CA279, etc are disclosed without benefit of sequence identifiers - SEQ ID NOs.

Furthermore PhKRS, I41 AND/OR S268 MUTANT OF PHΔAD, PhΔAD, I41, S268 are not assigned sequence identifiers in the text of the description or in the claims.

The sequence CUCUAAA or CUUCCUAA in claims 11 and 12 are not assigned sequence identifiers.

The sequences in Figures 1, 3 and 5 are not identified in the Brief Description of the drawings.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately using SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a

substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Appropriate correction/clarification is required.

Furthermore the disclosure is objected to because of the following informalities:

On page 1 [0004], line 7 the recitation: "a variety" is repeated.

On page 17, line 11, [0061], the word "acid" is misspelled.

On page 41, [0121, 0124] of the description, SEQ ID NO: 1 is identified as an orthogonal tRNA synthetase sequence, however SEQ ID NO: 1 is limited to a short nucleic acid sequence which appears in the sequence listing as a *Pyrococcus abyssi* lysyl tRNA.

On page 68, [0201], line 6 and 7 the recitation: "Reporter plasmids pAC-AK_{cuA} and pAC-AK_{cuA} show moderate toxicity as well, growing to 71% and 52%". This recitation is unclear. Are these two samples describing growth cultures comprising the same plasmid?

Although an examination of this application on the merits can proceed without prior compliance, compliance with the Sequence Rules is required for the response to this Office action to be complete.

Claim Objections

Claims 1-3, 6-13, 15-19, 21 and 22 are objected to because of the abbreviations O-tRNA and I41 AND/OR S268 MUTANT OF PHΔAD, PhΔAD, I41 and S268. Abbreviations must be written out in full in the first instance of their appearance. For examination purposes, the examiner will read the abbreviation I41 AND/OR S268 MUTANT OF PHΔAD, PhΔAD, as mutants of *Pyrococcus horikoshii* tRNA synthetase (PhKRS) and I41 and S268 as a mutant derived from PhΔAD.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6-13, 15-19, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 6-13, 15-19, 21 and 22 are drawn to a translation system comprising a genus of lysyl-O-tRNA and corresponding lysyl-O-RS from any source (including any bacteria, yeast, algae, human etc.) or comprising a genus of lysyl-O-RS and lysyl-O-tRNA and variants derived from *Pyrococcus horikoshii* (6-8) wherein the lysyl-O-RS preferentially charges the corresponding lysyl-O-tRNA or modified variant thereof with the unnatural amino acid, homoglutamine (claims 1-3, 6-13, 15-19, 21 and 22).

Furthermore these claims are drawn to a genus of lysyl-O-RS and lysyl-O-tRNA or modified variants thereof that suppress a stop or frame shift selector codon with an efficiency of at least 50% compared to the efficiency of the lysyl-O-RS of PhΔAD, or I41 and/or S268 mutants of PhΔAD in combination with the lysyl-OtRNA of SEQ ID NO: 26. The specification defines "a conservative variant of a lysyl-O-RS or lysyl-O-tRNA" are sequences having typically less than 5% variation. However the specification does not provide a correlation between a lysyl-O-tRNA with 5% variation and its function or the structure of a lysyl-O-RS with up to 15 amino acids variation and its function. Minor variations in the anticodon region of a tRNA or minor variations in the amino acid binding site of a synthetase can affect specificity for any given amino acid (natural or unnatural).

However the specification only teaches generation of a specific lysyl-orthogonal synthetase and lysyl-orthogonal tRNA (derived from archaeal tRNALys sequences) that selectively incorporates the amino acid homoglutamine (hGln) into myoglobin in response to the four-base codon AGGA.

Thus Applicants are not in possession of a translation system wherein any lysyl-O-RS and variants thereof that preferentially charge any lysyl-O-tRNAs with the unnatural amino acid, homoglutamine as encompassed in the claims.

The disclosure of a translation system comprising the lysyl-tRNA with the structure of SEQ ID NO: 26 and the synthetase mutants, PhΔAD, or I41 and/or S268 mutants of PhΔAD that are derived from *Pyrococcus horikoshii* lysyl tRNA synthetase is

insufficient to provide description for a translation system comprising the genus of lysyl-O-tRNA/ lysyl-ORS molecules broadly encompassed in the claims.

Thus the specification does not convey to the skilled artisan that Applicants were in possession of any lysyl-O-tRNA and or lysyl-O-RS molecules with any structure wherein said tRNA molecules can exhibit a suppressor efficiency of at least 50% in the presence of any cognate lysyl-O-RS from any source or with the O-tRNA synthetase of PhΔAD, or I41 and/or S268 mutants of PhΔAD and the O-tRNA of SEQ ID NO: 26.

The Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as structure, formula [or] chemical name, 'of the claimed subject matter sufficient to distinguish it from other material. " For claims drawn to a genus, MPEP § 2163 states the written description required for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by a disclosure of relevant identifying characteristics, sufficient to show that Applicants were in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus.

Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The specification does not teach any identifying characteristic or a structure/function correlation for a genus of lysyl-O-RS that can ensure preferential charging of the amino acid homoglutamine onto the lysyl-O-tRNA of SEQ ID NO: 26.

Furthermore Applicants are not in possession of the genus of lysyl-O-RS/lysyl-O-tRNA pairs that can suppress a stop codon or a frame shift selector codon with an efficiency of at least 50% compared to the suppressor efficiency of the lysyl-O-tRNA of SEQ ID NO: 26 and the lysyl-O-tRNA synthetase of I41 AND/OR S268 mutant of PhΔAD. The specification does not describe a specific efficiency for any lysyl-O-RS/lysyl-O-tRNA pair including the specific efficiency for the lysyl-O-RS/lysyl-O-tRNA pairs of SEQ ID NO: 26 and the lysyl-O-tRNA synthetase of I41 AND/OR S268 to provide a skilled artisan a point reference that can be used to identify other members of the genus through a screening assay.

Thus although the claims describe the structure of the lysyl-O-tRNA, the claims do not disclose the structure of the lysyl-O-RS to be used in conjunction with said lysyl-O-tRNA. Therefore, these claims encompass a genus of lysyl-O-tRNA and/or lysyl-O-RS molecules that fit a desired functional characteristic.

The disclosure of the structure of the lysyl-O-tRNA of SEQ ID NO: 26 and the recitation of a lysyl-O-tRS, I41 and/or S268 mutant of PHΔAD is not representative for the genus of lysyl-O-tRNA/lysyl-O-tRS claimed because, to fully describe a translation system comprising a genus of lysyl-O-tRNA/ lysyl-O-tRS, Applicants must (1) describe at least one species from the claimed genus of lysyl-O-tRNA/ lysyl-O-tRS pairs sufficient to be representative of said genus whereby a skilled artisan, can use the structure and efficiency of the pair as a point of reference to identify other members of the genus through an assay such as a screening assay thus predict the structure of other members encompassed in the claimed genus and (2) identify the common

characteristics when coupled with a known or disclosed correlation between function and structure, or a combination thereof.

Given this lack of description of representative species encompassed by the genus of the claim, the specification does not sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1-3, 6-13, 15-19, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because while the specification may be enabled for a translation system or a cell co-expressing the specific orthogonal tRNA synthetase of SEQ ID NO: 28, that preferentially charges the $tRNA^{lys}$ of SEQ ID NO: 26 with the unnatural amino acid homoglutamine, it does not provide enablement for a translation system or cell comprising any lysyl-tRNA synthetase that preferentially charges a homoglutamine on to the lysyl-O-tRNA of SEQ ID NO: 26 with an efficiency of at least 50% compared to the efficiently of said specific lysyl-O-RS in combination with the lysyl-O-tRNA of SEQ ID NO: 26.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988). The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working

example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

N.B. MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

In the instant case, the amount of direction and guidance provided is insufficient because the suppressor efficiency of a selector codon varies depending on the structure of the tRNA, the tRNA synthetase and the amino acid used. Applicants teach mutant lysyl-tRNA synthetases derived from *Pyrococcus horikoshii (PhRS)* and a lysyl-O-tRNA derived from a consensus of archaeal lysyl tRNA molecules (which was further altered by an insertion of a nucleic acid comprising CUCUAAA). Said orthogonal pair was used to incorporate the unnatural amino acid, homoglutamine into a protein of interest (myoglobin protein).

However the breadth of the claims encompasses a translation system or cell co-expressing any lysyl-O-tRNA and any tRNA synthetase and variants thereof from any

source having any sequence structure that preferentially charges said lysyl-O-tRNA with homoglutamine with an efficiency of at least 50% compared to the efficiency of a lysyl O-RS of I41 and/or S268 mutant of PHΔAD and a lysyl O-tRNA of SEQ ID NO: 26.

However Applicants have not taught how to make or use a translation system or cell that co-expresses any lysyl-O-tRNA and an lysyl-OtRNA synthetase comprising any structure wherein said lysyl-OtRNA synthetase preferentially charges said lysyl-O-tRNA with a homoglutamine.

Furthermore the standard for meeting the enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experiments required to identify lysyl-O-tRSs that preferentially charge a lysyl-O-tRNA with homoglutamine is enormous because the structure of the lysyl-O-RS to be used with the lysyl-otRNA of SEQ ID NO: 26 is not undefined. Thus for each structure of ORS used in conjunction with the OtRNA of SEQ ID NO: 26, the efficiency will vary.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the structure of the specific cognate lysyl-tRNA synthetase to be used with the O-tRNA of SEQ ID NO: 26 as a point of reference for comparing suppressor efficiency for the scope of lysyl-O-tRS and lysyl-O-tRNAs encompassed in the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAGNEW H. GEBREYESUS whose telephone number is (571)272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kagnew H Gebreyesus PhD/
Examiner, Art Unit 1656

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